REMARKS

Claims 16-31 are pending. Claims 16 and 21 have been amended to more clearly recite what Applicant believes to be the invention. Support is found at p. 4, lines 1 and 3. Amendments to the claims are shown in the attached "MARKED UP VERSION TO SHOW CHANGES MADE." An Appendix of the pending claims is attached for the Examiner's convenience. The following comments are put forth at this time in response to rejection of the claims. Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the present claims is respectfully requested for the reasons that follow.

Rejections Under 35 U.S.C. § 112, first paragraph

Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses.

Claim 29 is drawn to a library of cells intracellularly expressing randomized polypeptides. The Examiner states that there is no direction given between delivery of specific peptides to subcellular or intracellular organelles and the "random intracellular expression of a library of peptides." The Examiner further states that the claim lacks adequate support and constitutes new matter. Applicant respectfully disagrees.

First, the claim is not directed to "random intracellular expression," as the Examiner states. Rather, it is directed to intracellular expression of randomized peptides. "Intracellular" signifies within the cell. Thus, the claim refers to expression such that the expressed peptides are within cells.

Second, Applicant respectfully submits that the claim has full support, as can be seen throughout the specification. Applicant directs the Examiner's attention to the specification at p. 5, lines 12-13 ("candidate bioactive agents are introduced into the cells, and the cells express the

nucleic acids to form peptides"); p. 6, lines 8-9 ("which allow the localization of the candidate bioactive agent into a subcellular . . . compartment"); p. 9, lines 9 and 13-17 ("suitable targeting sequences include . . . signal sequences capable of constitutively localizing the candidate expression products to a predetermined cellular locale . . . ."); p. 17, Table I and line 16; p. 19, lines 14-16 ("Generally, the candidate nucleic acids are expressed within the cells to produce expression products of the candidate nucleic acids . . . .").

Additionally, Applicant wishes to reiterate the arguments presented in the response filed on September 27, 2001. At page 10, lines 21-22, the specification states, "the randomized expression product-containing region could be contained within a cytoplasmic region. . . ." At page 37, lines 14-18, the specification discusses a screen for "intracellular peptide activators" of a metastasis suppressor gene. At page 40, lines 28-31, the specification discusses screening "intracellular peptides" for agents that "block the expression or function of . . . oncogenes...." The title of the application itself points to screening for "intracelluar effector peptides."

Applicant respectfully submits that the claim is fully described in the specification and that no new matter was introduced by the amendment. Applicant requests, therefore, that the rejection be withdrawn.

Claims 16-28 and 30-31 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification is enabling for a molecular library of retroviruses comprising randomized nucleic acids encoding a plurality of randomized peptides, and is enabling for a cellular library containing a molecular library of retroviral constructs comprising randomized nucleic acids. However, the Examiner states that the specification does not reasonably provide enablement for a molecular library of retroviral constructs encoding a plurality of randomized peptides and the cellular library of retroviral constructs "integrated into cellular genome consisting of fusion partner." Further, the Examiner states that the specification does not enable one to make and/or use the invention commensurate in scope with these claims.

The Examiner concludes that undue experimentation would be required to practice the invention the claimed invention. Applicant respectfully traverses.

The Examiner considers several of the eight factors set forth in *In re Wands* for determining undue experimentation, namely:

(a) the breadth of the claims;
(b) the nature of the invention;
(c) the state of the prior art;
(d) the relative skill of those in the art;
(e) the predictability of the art;
(f) the amount of guidance or direction presented;
(g) the presence or absence of working examples; and
(h) the quantity of experimentation necessary.

Applicant considers each of the above factors and respond to the Examiner's comments regarding each factor as follows.

(A) The Breadth of the Claims

The Examiner states that the breadth of the claims is huge because of Applicant's failure to specifically claim the metes and bounds regarding the production of candidate bioactive agents expressed in the cellular library. Applicant disagrees.

Applicant first notes that the claims are not directed to the production of candidate bioactive agents; rather, the claims recite molecular and cellular libraries. The means of production of the claimed libraries is irrelevant to the breadth of the claims. The claimed libraries are produced by any method known in the art.

Second, the metes and bounds of the claims are clear.

(B) The Nature of the Invention/State of the Prior Art

The Examiner states that the invention is broadly directed to a method and compositions for screening for a candidate bioactive agent and accesses molecules or targets within living cells and provides for the selection of these bioactive agents with desired phenotypic effects. The Examiner concludes that critical or essential parameters to practice the invention but not included

in the claims are not enabled by the disclosure, and cites *In re Mayhew* 188 USPQ 356 (CCPA 1976) and *Ex parte Bide* 42 USPQ2d 14 (Bd. Pat. App. & Int.).

Applicant first notes that the claims are not directed to methods. The claims are directed to molecular and cellular libraries. The libraries comprise retroviral constructs comprising randomized nucleic acids which encode randomized peptides. The cellular libraries comprise retroviral constructs which may be integrated into the cellular genome.

Applicants wish to point out that claims directed to screening methods are included in parent applications U.S.S.N. 08/589,109, filed January 23, 1996, now U.S. Patent No. 6,365,344; U.S.S.N. 08/787,738, filed January 23, 1997, allowed; and U.S.S.N. 08/789,333, filed January 23, 1997, now U.S. Patent No. 6,153,380.

With regard to the Examiner's statement that essential parameters are not included in the claims, Applicant notes that the Examiner has not provided a formal rejection based on this assertion.

(C) The Relative Skill of Those in the Art

The relevant art area with regard to the claimed invention is the field of molecular biology. Applicant submits that the level of skill in the art is high.

(D) The Predictability of the Art

Applicant submits that the field of molecular biology as it relates to molecular and cellular libraries is high.

(E) The Amount of Direction/Working Examples

The Examiner states that the specification only provides guidance and examples directed to the method of obtaining a cellular library containing a molecular library of retrovirus constructs wherein the construct is integrated into the cellular genome encoding a plurality of randomized peptides. The Examiner further states that it does not provide enough guidance as to the specific genomes or a specific sequence of molecules which would selectively be inserted to encode a specific peptide. The Examiner states, "this is not representative of the scope of

claimed methods, for screening and selecting a candidate bioactive agent envisioned to have pharmacological applications."

Applicant notes that the claims are not directed to methods, as the Examiner has characterized them. The claims are directed to molecular and cellular libraries.

Applicant submits that the specification provides detailed guidance for producing the claimed molecular and cellular libraries. For example, guidance is provided in specification for molecular and cellular libraries at Figure 1, Figure 2 and Figure 4; page 2, lines 22-24 (listing retrovirus method references); p. 23, lines 22-28 and p. 24, lines 7-11 (describing recombinant retrovirus systems and listing several references); p. 24, line 12 to p. 26, line 10 (providing description of production of retroviral constructs comprising randomized nucleic acids); p. 26, line 11 to p. 28, line 21 (providing description of retrovirus production systems); p. 28, line 22 to p. 29, line 7 (providing description of retrovirus concentration). Further guidance with regard to cellular libraries is provided a p 29, line 8 to p.30, line 2 (describing introduction of retrovirus into cells and listing cells).

Additionally, knowledge of specific genomes is not required to practice the claimed invention; similarly, knowledge of specific sequences is not required to practice the claimed invention.

(F) Quantity of Experimentation

The Examiner states that the specification lacks representative examples regarding the method of obtaining randomized nucleic acids encoding a plurality of randomized peptides and fusion partners of a representative sample of a set of molecules, and concludes that the amount of experimentation would be undue.

Applicant disagrees. The specification provides a detailed example at p. 69, beginning at line 20, describing the construction of a random peptide library in a retroviral vector. Figures 1, 2 and 4 further support the description of the example. Furthermore, the specification provides detailed description of randomized nucleic acid synthesis at p. 19, line 22 to page 22, line 28.

Applicant submits that undue experimentation would not be required to practice the claimed invention.

Applicant disagrees with the Examiner's characterization of the invention. Further, in light of the high level of skill in the art, the nature of the invention, the predictability in the art, and the detailed teaching of the specification, Applicant asserts that undue experimentation would not be required to practice the full scope of the claims. Applicant respectfully requests that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 16-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully traverses the rejection.

The Examiner states that "randomized peptides" and "randomized nucleic acids" are vague, covering an enormous field. The Examiner further states that "constructs" and "cellular genome" lack sufficient information on specific structure, sequence or other identifying characteristics.

Applicant reminds the Examiner that the requirement under 35 U.S.C. 112, second paragraph, depends on whether the scope of the claim is clear to a person of ordinary skill in the art. See MPEP 2171. Further, breadth of a claim is not to be equated with indefiniteness. See MPEP 2173.04; *In re Miller*, 169 USPQ 597 (CCPA 1971). Thus, inasmuch as the Examiner's rejection depends on a finding of undue breadth, the rejection is improper under 35 U.S.C. 112, second paragraph.

The scope of the terms "randomized peptides" and "randomized nucleic acids" is clearly understood from the specification. The terms are defined at p. 19, lines 20-22: "By 'randomized' or grammatical equivalents herein is meant that each nucleic acid and peptide consists of essentially random nucleotides and amino acids, respectively."

Likewise, the scope of the terms "constructs" and "cellular genome" in claim 22 is clear. The term "constructs" has an art-recognized meaning, i.e. nucleic acid vectors fused to one or more added nucleic acid components. In claim 22, "constructs" refers specifically to the "retroviral constructs" recited in claim 21. As understood by one of skill in the art, a retroviral construct is a retroviral nucleic acid vector comprising one or more added nucleic acid components. The "construct" of claim 22, therefore, refers to a retroviral nucleic acid vector fused to a randomized nucleic acid sequence. Further, a retroviral construct is exemplified in Figure 4 of the specification.

The term "cellular genome" similarly is clear in scope. The term "genome' has an art-recognized meaning. "Genome" refers to all of the genes of a haploid cell of a given organism, replicated when the cell divides. Thus, the scope of the term is clear to one of skill in the art.

Additionally, as stated previously, breadth of a claim is not to be equated with indefiniteness. See MPEP 2173.04; *In re Miller*, 169 USPQ 597 (CCPA 1971). Inasmuch as the Examiner's rejection depends on a finding of undue breadth, the rejection is improper under 35 U.S.C. 112, second paragraph.

Applicant submits, therefore, that the terms are defined with sufficient clarity in the art to provide one of skill in the art with a clear understanding of the claim's scope. Applicant respectfully requests that the rejection be withdrawn.

Claims 23-27 are rejected under 35 U.S.C. 112, second paragraph.

The Examiner finds that the fusion partner consists of "a targeting sequence", "a rescue sequence", "a stability sequence" and "a dimerization sequence." The Examiner states these fusion partners are each different from one another and consist of many variations in each group, not disclosed sufficiently in the specification, and further states that the class is enormous.

Applicant has assumed for the purposes of responding to this rejection that the Examiner is rejecting the claims based on a finding that the term "fusion partner" is indefinite. Applicant traverses the rejection.

Applicant submits that the term "fusion partner" is clear in scope from the specification. "Fusion partner" is defined in the specification at page 6, lines 2-4: "By 'fusion partner' . . . herein is meant a sequence that is associated with the candidate bioactive agent, that confers upon all members of the library in that class a common function or ability." The description goes on to explain that "fusion partners" comprise presentation structures, targeting sequences, rescue sequences, stability sequences, dimerization sequences, combinations of these, and linker sequences. See p. 6, lines 4-15.

Applicant submits that the term is clearly defined and that one of ordinary skill in the art would understand the scope of the claim. Additionally, inasmuch as the Examiner's rejection depends on a finding of undue breadth, the rejection is improper. As stated above, breadth of a claim is not to be equated with indefiniteness. See MPEP 2173.04; *In re Miller*, 169 USPQ 597 (CCPA 1971).

Rejections Under 35 U.S.C. § 103(a)

Claims 16-22 and 28-31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Jellis et al. in view of Kaufman and Druker et al. Applicant respectfully traverses.

Jellis et al. (Gene 137:63-68 (1993)) concerns a phage display library and discloses unique nucleic acids encoding approximately 1.5 $x10^8$ unique peptides of 20 amino acids fused to coat proteins for display on the surface of phage particles. The emphasis in Jellis et al. is the creation of unique peptides with minimal amino acid bias. Jellis et al. do not disclose expression in a retroviral vector. Finally, Jellis et al. do not disclose biased randomized nucleic acids.

With regard to cellular libraries, Jellis et al. do not disclose a cellular library (claims 21-22 and 29-31). Jellis et al. do not disclose a cellular library wherein the retroviral constructs are

integrated into the cellular genome. Jellis et al. also do not disclose cellular libraries intracellularly expressing randomized peptides.

Kaufman is a general reference about using a variety of mammalian expression vectors for gene expression in mammalian cells. Kaufman teaches that retroviral vectors can be used to introduce genes into a variety of host cell types, and that genes so introduced may incorporate into the host genome. Kaufman, however, does not teach using retroviral vectors for creating a library. Kaufman also does not teach or suggest expression of random peptides. In fact, Kaufman is focused on the use of retroviral vectors generally to express cDNA (non-random). See, e.g., p. 487 ("for the expression of a gene obtained from a higher eukaryote"), p. 494 ("expression of genes introduced by retroviral infection"), and p. 506 ("Efficient Vectors for Expression of cDNAs in Mammalian Cells"). Kaufman does not teach or suggest molecular libraries having biased randomized nucleic acids. With regard to cellular libraries. Kaufman also does not teach cellular libraries intracellularly expressing randomized peptides.

Kaufman, in fact, teaches away from the combination of random peptides for expression in a retroviral vector. As discussed further below, Kaufman states that expression from retroviral vectors is low, that there are problems w/RNA splicing etc., and that different DNA sequence inserts may impair propagation of expression, resulting in variable success.

Druker et al. disclose a collection of retroviruses with inserts encoding polyoma middle T antigens each having single point mutations. Druker demonstrates that the polyoma middle T antigen inserts can be expressed in a retroviral system, but does not disclose nor suggest expression of random peptides in a retroviral system. The peptides disclosed by Druker represent middle T antigen peptides, each having a single random mutation. Applicant notes that these peptides are not "randomized" as defined in the present specification. Nor are the peptides of Druker "biased in their randomization," as defined in the specification. Further, Druker does not disclose a library having at least 10^4 different random nucleic acids.

As stated in the MPEP at §2143, in order to support a *prima facie* case of obviousness under 35 U.S.C. §103(a), the prior art, either individually or in combination, must satisfy the following three elements: 1) there must be some motivation or suggestion, either in the references or in the knowledge available to one skilled in the art, to modify or combine the references to practice the claimed invention; and 2) there must be a reasonable expectation of success; and 3) the prior art references when combined must teach or suggest all of the claim limitations. Applicant respectfully submits that the cited prior art references do not render the present invention obvious.

The Examiner states the motivation to combine the references arises from "the well known technique of gene transfer through retrovirus which is a high [sic] efficient method." Applicant disagrees.

Applicant submits that knowledge of a technique is not appropriate motivation to combine references. Applicant respectfully reminds the Examiner that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed.Cir. 1990). Additionally, a statement that modification of the prior art would have been well within the ordinary skill of the art because the references teach that all aspects of the claimed invention were individually known is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *See Ex parte Levengood*, 28 USPQ2d 1300 (Bd.Pat.App. & Inter. 1993); MPEP §2143.01. As the Federal Circuit made clear in *In re Lee*, 61 USPQ2d 1430, 1435 (2002), " 'common knowledge and common sense,' . . . do not substitute for authority. . . ." Further, " 'deficiencies of the cited references cannot be remedied by . . . general conclusions about what is 'basic knowledge' or 'common sense.' " *Id.* at 1434-35.

Also, as acknowledged by the Examiner, Jellis et al. do not disclose libraries of retroviruses or cells containing libraries. Furthermore, it is not certain from Jellis that random

nucleic acid inserts will successfully encode novel peptides in a retroviral system. Kaufman does not add any motivation for the creation of random peptide libraries, and in fact teaches away from such a library. Kaufman states that expression in retroviral-based vectors has met with variable success due to "problems with RNA splicing and mRNA translation" and because "insertion of different DNA sequences may impair propagation or expression of the recombinant retrovirus." (p. 495, top). Druker et al. do not add any motivation.

To summarize, none of the cited references, taken alone or in combination, provide the motivation to make retroviral random peptide libraries.

Additionally, there is no reasonable expectation of success. Kaufman, as discussed above, teaches away from the combination of references. Given this, the reasonably skilled artisan would not have a reasonable expectation of success in arriving at the instant invention given the cited references and knowledge available in the art at the time of filing.

Rejection concerning Nilsson

Claims 23-27 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Jellis et al. in view of Kaufman, Druker et al., and Nilsson et al. Applicant respectfully traverses.

Jellis et al., Kaufman, and Druker et al. are discussed *supra*.

Nilsson et al. teaches the construction of fusion proteins for a variety of purposes. However, Nilsson et al. does not cure the defects of Jellis, Kaufman, and Druker.

The Examiner states that it would be *prima facie* obvious to combine the teachings of Nilsson with Jellis, Kaufman, and Druker "to access molecules or targets within living cells for variety of reasons ranging from protein recovery to therapeutic uses." However, Jellis, Kaufman, and Druker do not provide adequate suggestion to combine their teachings to obtain the claimed molecular and cellular libraries, as discussed above. Nilsson does not cure the deficiencies of these references, and therefore, the combination of Nilsson with Jellis, Kaufman, and Druker cannot provide for a *prima facie* case of obviousness.

Applicant submits that motivation or suggestion to combine or modify the cited references to practice the claimed invention is not provided by the references or by knowledge in the art, and that a reasonable expectation of success in arriving at the instant invention is not provided. Accordingly, Claims 16-28 are not obvious under 35 U.S.C. §103(a), and Applicant requests withdrawal of the rejections.

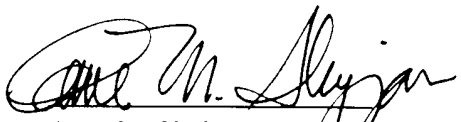
CONCLUSION

Applicant respectfully requests favorable consideration of the preceding arguments and acceptance of the claims as currently pending. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

Date: July 11, 2002



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MARKED UP VERSION TO SHOW CHANGES MADE

The claims have been amended as follows:

16. (Twice Amended) A molecular library of retroviruses comprising <u>retroviral constructs, each construct comprising a</u> [at least 10^4 different] randomized nucleic acid[s] encoding a [plurality of] randomized peptide[s], <u>wherein said molecular library comprises at least 10^4 different randomized nucleic acids</u>.

21. (Twice Amended) A cellular library of mammalian cells containing a molecular library of retroviral constructs, [said molecular library comprising at least 10^4 different] <u>each construct comprising a</u> randomized nucleic acid[s] encoding a [plurality of] randomized peptide[s], <u>wherein said molecular library comprises at least 10^4 different randomized nucleic acids</u>.

Appendix: Pending Claims

16. (Twice Amended) A molecular library of retroviruses comprising retroviral constructs, each construct comprising a randomized nucleic acid encoding a randomized peptide, wherein said library comprises at least 10^4 different randomized nucleic acids.

17. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^5 different randomized nucleic acids encoding a plurality of randomized peptides.

18. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^6 different randomized nucleic acids encoding a plurality of randomized peptides.

19. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^7 different randomized nucleic acids encoding a plurality of randomized peptides.

20. (Amended) A molecular library of retroviruses according to claim 16 comprising at least 10^8 different randomized nucleic acids encoding a plurality of randomized peptides.

21. (Twice Amended) A cellular library of mammalian cells containing a molecular library of retroviral constructs, each construct comprising a randomized nucleic acid encoding a randomized peptide, wherein said molecular library comprises at least 10^4 different randomized nucleic acids.

22. A cellular library according to claim 21 wherein said constructs are integrated into the cellular genome.

23. A molecular library of retroviruses according to claim 16, wherein said nucleic acids further encode a fusion partner.

24. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a targeting sequence.

25. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a rescue sequence.

26. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a stability sequence.

27. A molecular library of retroviruses according to claim 23, wherein said fusion partner comprises a dimerization sequence.

28. A molecular library of retroviruses according to claim 16, wherein said randomized nucleic acids are biased in their randomization.

29. A cellular library of mammalian cells containing a molecular library of retroviral constructs, said library of cells intracellularly expressing at least 10^4 randomized peptides.

30. (New) A cellular library of mammalian cells containing a molecular library of retroviral constructs, said library of cells intracellularly expressing at least 10^4 randomized peptides, wherein said each of said peptides is linked to a fusion partner.

31. (New) A cellular library according to claim 30, wherein said fusion partner comprises a rescue sequence.